

The Role of Genetic and Environmental Factors in the Etiology of Type 2 Diabetes.

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Abstract

Diabetes is an endocrine disease characterized by a full or relative reduction in the offspring of insulin in connection with diabetes. The metabolism of carbohydrates is not only disturbed, but other disorders are also manifested in the body. Its general properties are: an increase in the amount of sugar in the blood serum and, as a result, glucose intolerance. Diabetes treatment should be done without failure and only under the supervision of specialists. Umbilical disease is characterized by characteristics and high levels of glucose. Several causes were found, including the genetic or genetic factor that contributes a large percentage, including the operations of the whole genome. A number of genes are associated with diabetes.

Keywords :- Diabetes, genetic, Etiology, predisposition, GDM

1. Introduction

It is a disease that manifests itself in high blood sugar levels due to insufficient exposure to insulin. Insulin is a hormone secreted by the pancreas, more specifically by beta cells in Langerhans islets. In diabetes, it is either completely absent the body's cells do not respond adequately (type 2 diabetes, or non-insulin-dependent diabetes). Insulin is a hormone that regulates the metabolism, especially carbohydrates (sugars), but also fats and proteins". [1] in diabetes mellitus, due to insufficient exposure to insulin, a complex metabolic disorder occurs, the blood sugar content rises (hyperglycemia), sugar is excreted in the urine (glucose), and acidic products appear to impair the combustion of fats in the blood. [2] The

causes of diabetes are not fully understood. Genetic predisposition, autoimmune beta cell lesions of the pancreas, infectious diseases are important (some viruses are thought to be able to infect beta cells). Also, diabetes can develop as a complication of pancreatitis, shock, or a pancreatic tumor, hypercortisolism, and ingestion of corticosteroid hormones and progestogens. Conditions of detention (lack of physical activity, obesity, chronic diseases) play an important role in the development of diabetes. [3] Early manifestations usually include urination, thirst, increased appetite, and despite this, weight loss, and weakness. Initially, the extra weight drops quickly for no apparent reason. Late signs - loss of appetite, vomiting, depression, lethargy and drowsiness - are associated with the development of ketoacidosis. [4] The examination reveals thinning back muscles, greasy hair, and dandruff, which is especially typical for cats. Less commonly, cataracts and a "confused" gait (a consequence of diabetic neuropathy) are found. [5] To make a definitive diagnosis of diabetes, it is not sufficient to reveal any of the signs mentioned above, as each of them can be caused by many other causes besides diabetes. So, for example, frequent urination and thirst can be caused by chronic kidney failure, blood glucose levels can rise under the influence of stress, and cataracts can simply be dementia. [6] Response Molecular biological methods of diagnosing diabetes mellitus are constantly being improved and introduced into clinical practice and All data obtained should be evaluated with a geneticist, taking into account other clinical and laboratory data. [7]

1.1-Etiology

- **Type 1 diabetes**

Insulin isn't created because of immune system annihilation of pancreatic beta cells In type 1 diabetes (recently called adolescent or insulin subordinate), immune system obliteration of pancreatic beta cells (perhaps because of natural factors in hereditarily powerless people) prompts a deficiency of insulin discharge. For a while or years, this obliteration isn't shown clinically, until the beta-cell check diminishes so much that the insulin focus gets inadequate to control glucose However, this sort of diabetes additionally happens in grown-ups (inert immune system diabetes in grown-ups, which is regularly mistaken for type 2 diabetes from the outset). [8] Type 1 diabetes normally shows up in youth and puberty, and up to this point was the most widely recognized type of diabetes analyzed in individuals more youthful than 30 years of age. A few instances of type 1 diabetes (particularly in non-white individuals) don't seem, by all accounts, to be an immune system sickness and are viewed as of obscure reason. Type 1 diabetes represents under 10% of all diabetes cases [9] .The pathogenesis of immune system obliteration of beta cells is identified with ineffectively comprehended

communications between inclination qualities, autoantibodies, and ecological elements [10]. The qualities for inclination to diabetes have a place with the fundamental histocompatibility complex, particularly HLA-DR3, DQB1 * 0201, HLA-DR4, and DQB1 * 0302 (present in over 90% of patients with type 1 diabetes), and are likewise present outside of this compound. [11] The last seems to control insulin amalgamation and handling and, in blend with MHC qualities, decide the danger of creating diabetes. Inclination qualities are more normal in certain populaces than in others, which clarifies high AV of T1D among delegates of certain ethnic gatherings (Scandinavians, Sardinians) [12].

The autoantigens are acidic glutamic carboxylase, insulin, proinsulin, linked protein molecule, The development of type 1 diabetes often occurs after infection with a number of viruses (coxsackie, rubella, Epstein-Barr viruses, retroviruses). Viruses can infect and destroy beta cells directly, or lead to indirect damage to these cells by exposing self-antigens, activating endogenous lymphocytes, stimulating the immune response by mimicking autoantigens (molecular mimicry), or other mechanisms [13,14].

- **Type 2 diabetes**

In type 2 diabetes (recently called grown-up diabetes,), insulin emission is inadequate, on the grounds that insulin patients create obstruction. Insulin obstruction in liver tissues prompts a deficiency of the capacity to restrain glucose creation in the liver, and insulin opposition in fringe tissues hinders glucose retention. The blend of these elements prompts both fasting and postprandial hyperglycemia. Insulin levels are regularly high, particularly toward the start of the infection. In the later phases of the infection, insulin creation may diminish, demolishing hyperglycemia [16] The sickness normally creates in adulthood, with its predominance expanding with age. Hindered glucose resistance is found in up to 33% of grown-ups beyond 65 years old, Postprandial plasma glucose levels rise more in the older than in more youthful grown-ups, particularly in the wake of eating a feast wealthy in carbs Also, glucose levels drop to the typical reach for a more extended period, particularly because of development of instinctive and stomach fat and diminished bulk [17] .Type 2 diabetes is progressively basic among youngsters as youth heftiness has gotten a plague. In grown-ups, over 90% of instances of type 2 diabetes happen. The inescapable sort 2 diabetes among some ethnic gatherings (Amerindians, workers from Spain and Asia) and among patients' family members plainly shows the presence of hereditary determinants of this illness. Albeit lately, no hereditary polymorphism has been discovered, that is, a solitary quality answerable for the more normal types of type 2 diabetes [18] .The pathogenesis of type 2 diabetes is perplexing and not completely comprehended. Hyperglycemia happens when insulin emission can

presently don't make up for insulin opposition. In spite of the fact that insulin obstruction is normal for patients with type 2 diabetes and those in danger, there is proof of beta-cell anomaly and debilitated insulin emission in these cases, including disability of the main period of its discharge in light of intravenous glucose, drive. Physiological insulin emission, expanded insulin discharge demonstrating hindered insulin preparing, amassing of amyloid glycoprotein in the islets of the pancreas (which is normally discharged with insulin) , High glucose can meddle with insulin emission, as high glucose levels lessen the affectability of beta cells and/or weaken their capacity (glucose harmfulness) These progressions as a rule create against the foundation of insulin opposition over numerous years [19].

Table 1- Criteria for compensation of carbohydrate metabolism in diabetes

Indicators	Compensation	Subcompensation	Decompensation
	T1D		
HbA1c	6,0-7,0	7,1-7,5	Above 7,5
Fasting glycemia, mmol / l	5,0-6,0	6,1-6,5	Above 6,5
Glycemia 2 h after meals	7,5-8,0	8,1-9,0	Above 9,0
	T2D		
HbA1c	6,0-6,5	6,6-7,0	Above 7,0
Fasting glycemia, mmol / l	5,0-5,5	5,6-6,6	Above 6,5
Glycemia 2 h after meals	Below 7.5	7,5-9,0	Above 9,0

Obesity acquire are two significant conditions for creating insulin obstruction in type 2 diabetes, Genetic elements might be at the base of stoutness, however diet, practice power and general way of life likewise assume a significant part. The body can't stifle lipolysis in fat

tissue, so free unsaturated fats are delivered from it, and an increment in their level in plasma can upset the incitement of insulin, glucose transport and the action of glycogen synthase in the muscles. Fat tissue additionally works as an endocrine organ, discharging into the blood numerous variables (adipocytokines) that decidedly (adiponectin) or adversely (tumor necrosis factor alpha, IL-6, leptin, resistin) impact glucose digestion. Deferred intrauterine development and low birth weight are likewise connected with the improvement of insulin opposition further down the road, which may mirror the unfavorable pre-birth impacts of natural components on glucose digestion [20].

1.2 Molecular access for studying genetic readiness of Type 2 diabetes

As of late a novel philosophy has been made to rank the up-and-comers in the T2DM associated genomic locale as possible ailment characteristics, which relies upon the spaces of the interfacing proteins of the contamination characteristics and thusly creating association subjects which address express natural limits and hence give an information concerning the physiological occupation of explicit up-and-comer. The etiology of T2D, anyway not satisfactory, incorporates various pathways wherein each conceivable contamination quality gives just a humble danger. Along these lines, to comprehend the illness pathophysiology it is smarter to investigate the worldwide collaboration network than single quality personalities [23]. These communications whenever utilized to focus on qualities may significantly expand the opportunity of recognizing illness qualities [24].

[25]. Despite the fact that the etiology and pathogenesis of GDM are similar to those in other types of diabetes mellitus (DM), a number of studies indicate that the molecular genetic mechanisms of these diseases can differ significantly. pathogenesis of GDM and other types of diabetes. It is known that increased insulin resistance and changes carbohydrate metabolism - normal physiological changes during pregnancy [26]. Exactly these features of carbohydrate metabolism during pregnancy, which, according to a number of authors "natural stress", can provoke the development of GDM in women with a genetic predisposition to diabetes. The pathogenetic proximity of GDM and other types of diabetes is also evidenced by the fact that in the late period after childbirth (5-12 years) 14.7% of women with a history of GDM develop DM1 and more than 20% - DM2 [27]. According to some observations, the incidence of T2DM in women who have undergone GDM, further increases by more than 7 times. Studies of the metabolome (a spectrum of proteins in serum and various tissues) in patients with GDM and other forms of diabetes revealed a significant similarity in biochemical disorders of the cardiovascular, respiratory and metabolic systems in such patients.[28] This similarity suggests the presence of common gene networks and molecular

mechanisms, provoking the development of GDM in women with latent forms of diabetes that can be identified only with the help of special laboratory research methods. Obviously, endogenous and exogenous factors provoking the development of T1DM and T2DM, simultaneously act as factors of predisposition. Taking into account the pathogenetic similarity of GDM with T2DM, GDM can be considered as a typical multifactorial disease in the development of which involves numerous genetic and exogenous factors. Predisposition genes, individual damaging effect which is not great, with unfavorable combinations several functionally weakened (recessive) variants and damaging exogenous factors can cause the development of the disease. Recessive forms of GDM are polymorphic. According to modern concepts, they are associated with several dozen genes, many (but not all) of which are identical to T2DM candidate genes.[29] (case-control) single polymorphic sites in patients with GDM, and in generalized analysis

the results of such studies. As a result of a meta-analysis of 10,336 cases of GDM and 17,445 cases of normal pregnancies, a non-random association with GDM and T2DM of seven genes was confirmed: T-cell transcription factor-7, encoding the nuclear receptor β -catenin, an activator signaling pathway (TCF7L2); melatonin 1B receptor (MTNR1B); mRNA binding protein insulin-like growth factor 2 (IGFBP2); Kir6.2 protein, which is one of two subunits ATP-dependent potassium channels (KCNJ11); regulatory subunit-1 of cyclin-dependent kinase type 5 (CDKAL1); alpha subunits of the potassium channel (KCNQ1) and glucokinase (GCK) [30]. Together with however, there was no association with the GDM of the receptor gene peroxisome proliferator gamma 2 (PPARG2) linked to T2DM, which indicates differences molecular mechanisms of these diseases. Genome-wide association analysis (GWAS) confirmed the linkage of GDM with a number of previously studied genetic loci, and also identified new genes for susceptibility to GDM and SD2. Thus, which included 468 pregnant women with GDM and 1242 women with uncomplicated pregnancy, confirmed the presence of common genes associated with both T2DM and GDM. These are the IGF2BP2 genes, TCF7L2, GCK, KCNQ1, insulin receptor (INSR), substrate insulin receptor-1 (IRS1), a transcription factor of the signaling pathway that regulates pancreatic development in embryogenesis (HHEX). Particularly strong adhesion to GDM was noted for genes CDKAL1 and MTNR1B, which, according to earlier data, are associated only with T2DM, the presence of common candidate genes in T2DM and GDM not confirmed in all studies. Analysis works performed over a 10-year period (1990—2011) in different populations showed that out of 20 genes linked to T2DM, only 3 are associated with GDM: TCF7L2, KCNQ1 and CDKAL1, which proves great variability of trigger mechanisms GDM [16]. The reasons for this are not

fully understood. Not it is excluded that to some extent they reflect the differences in the criteria for the selection of groups of patients with GDM and T2DM in different studies, [31]. Currently mutations of the MODY subtype have been identified, which proves a significant contribution these monogenic forms in the development of GDM The most common of these are variants due to mutations in the glucokinase gene (GCK) and in the hepatocyte nuclear factor 1A gene (HNF1A)

Gene ID	Gene Name	Chromosome Location	Genomic Region	Function
TCF7L2	Transcription factor 7-like2	10q25.3	Intron3,4,7	Blood-glucose homeostasis
CAPN10	Calcium-activated cysteine protease	2q37.3	Intron 3,6,13	Insulin secretion and action
PPAR γ	Peroxisome proliferator-activated receptor gamma	3p25	Exon 2	Adipocyte differentiation
KCNJ11	Potassium inwardly rectifying channel	11p15.1	Exon,Promoter,3 ¹ UTR	Regulation of glucose induced insulin secretion
LPL	Lipoprotein lipase	8p22	Intron3,Promoter region	Insulin secretion and action
PPP1R3	Protein phosphatase1 regulatory subunit 3	7q31.1	Intronic region	Glycogen metabolism
KCNJ10	Potassium inwardly-rectifying channel, subfamily J, member 10	1q22-23	Intron,Promoter region	Insulin secretion
IL6	Interleukin -6	7p21	Promoter region	Insulin resistance
ENPP1 (PC-1)	Ecto nucleotide pyro phosphate	6q22-q23	Exon 4	Insulin receptor signaling
GLUT10/SLC2A10	Glucose Transporter 10	20q12-13.1	Exon,Intron	Glucose metabolism
IPF 1	Insulin promoter factor 1	13q12.1	Regulatory elements	Transcription Factor
HNF1B/TCF2	Hepatocyte nuclear factor 1-Beta	17q12	Exon 4,7	TranscriptionFactor expressed in pancreatic β cell
HNF4A	Hepatocyte nuclear factor 4-alpha	20q12-13.1	Intron2,Promoter region	Development of pancreas
PGC-1 α	Peroxisome proliferator Activated receptor γ co-activator - 1 alpha	4p15.1	Exonic,3 ¹ UTR	Transcription co-activator
IRS-1	Insulin receptor substrate 1	2q35-36.1	Exonic region	Insulin signalling
KCNQ1	Potassium voltage-gated channel, KQT-like subfamily, member 1	11p15.5	Intron 15	Insulin secretion
RBP4	Retinol binding protein	10q23-24	Promoter region	glucose uptake in adipocytes to systemic insulin resistance
PTPN1	Protein Tyrosine Phosphate	20q13.13	Intron 1	Insulin Signalling
CETP	Cholesteryl ester transferase	16q13	Intron1 Exon 15	Lipid metabolism
APOE	Apolipo protein	19q13	-	Lipid metabolism
GLUT2	Glucose transporter 2	3q26	Promoter region	Glucose uptake in pancreatic β cells & liver

Figure 1-Names of the candidate genes studied for T2DM, along with chromosome location, genomic region and function

Table 1- Linkage results of various genome with TD

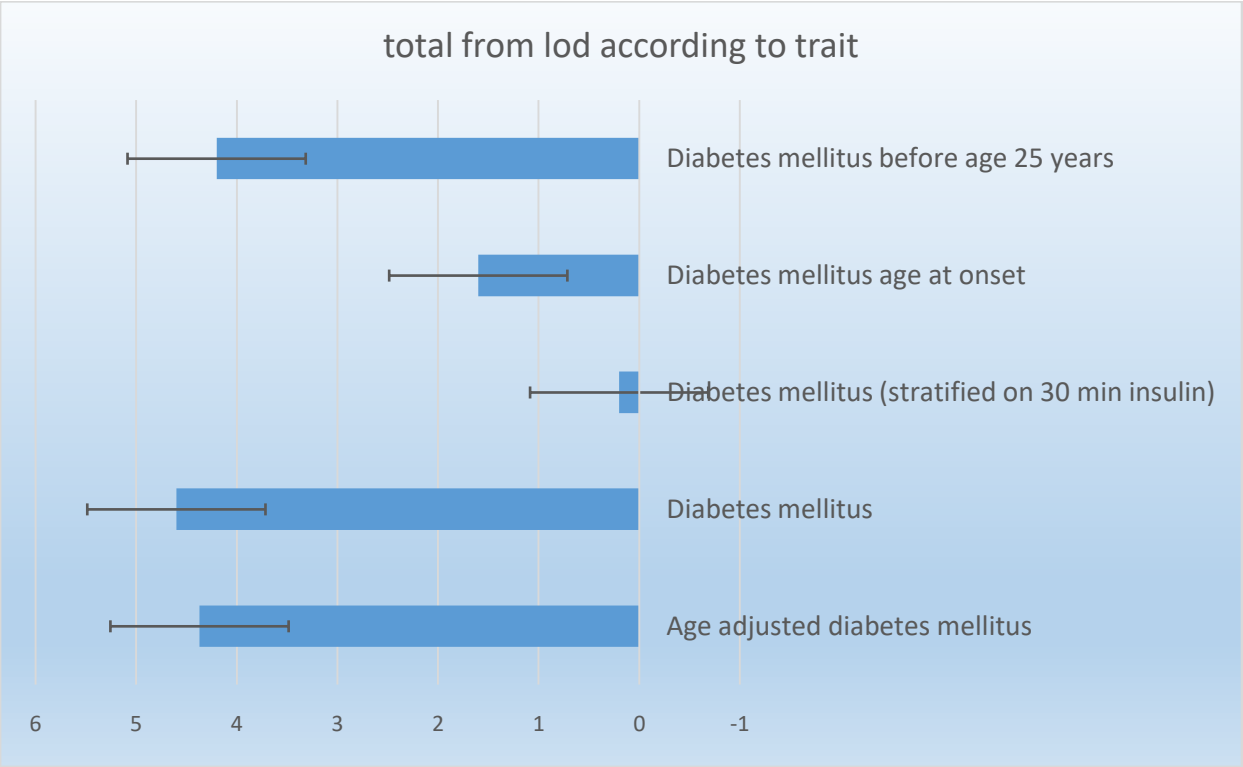
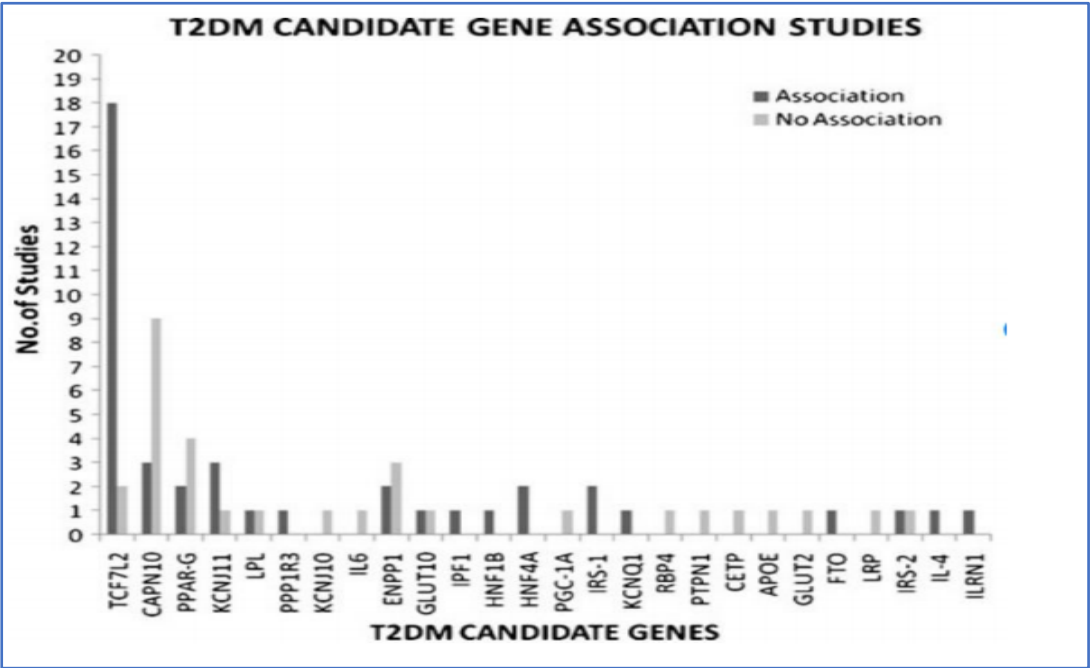


Figure 2- represents a bar diagram showing the number of studies with and without association between T2DM and different candidate genes



1.3 Conclusion

The search for genetic markers of GDM is promising for identifying pregnant groups high risk of developing GDM in early pregnancy. The solution to this problem will allow to carry out effective preventive measures, and in the case of GDM, to give an objective assessment of the progression of the disease, to optimize the correction of carbohydrate metabolism disorders and outcomes.

for both a pregnant woman and a newborn Improvement of approaches to molecular genetic analysis and implementation of effective and sufficiently economical methods of whole genome sequencing opens up new possibilities for studying the molecular mechanisms of GDM development and identifying the individual characteristics of the etiology and pathogenesis of this disease, which plays a key role in the development of effective personalized prevention and treatment methods this frequent complication of pregnancy. The significant test in distinguishing the fundamental hereditary reason for T2DM is the association of an enormous number of qualities with little impacts and the variable articulation of a portion of the qualities in various conditions furthermore, ethnic gatherings. In spite of fast upgrades in sub-atomic hereditary procedures empowering us admittance to huge range of hereditary data, the expected job of numerous competitor qualities engaged with the pathogenesis of T2DM remains indistinct, albeit some steady discoveries are gotten through applicant quality methodology. The need of great importance is to configuration proper GWA concentrates with huge example size in distinctive ethnic and temporary gatherings/populaces.

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